Heart pathology in rheumatic heart disease

Jacob J. Brenneman
University of Nebraska Medical Center

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HEART PATHOLOGY
IN RHEUMATIC HEART DISEASE

J. James Brenneman

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DEFINITION

Cecil, (1). "Rheumatic fever is a disease, probably infectious, and apparently closely associated with invasion of the body by hemolytic streptococci; it is characterized by febrile and toxic states, by the presence in various parts of the cardiovascular system and joints of multiple disseminated focal inflammatory lesions and at times by serofibrinous inflammation of some of the great mesothelial lined body cavities and joints; it is further characterized by a tendency for the febrile, toxic and arthritic signs to disappear following the exhibition of certain antipyretic drugs in sufficient doses."
INTRODUCTION and HISTORY

It is estimated that the disease occurs in about fifteen hundred to two thousand per million of population. Available statistics and clinical impressions indicate a falling incidence of rheumatic polyarthritis; with a corresponding decrease in rheumatic heart disease. The greatest ravages are in children and young adults, individuals who should be economic assets rather than liabilities.

Romberg, (2), in 1894 is generally considered the first to have described the inflammatory lesions in the myocardium now known as Aschoff bodies. However, Goodhart, (3), in 1879 really described the body. He observed interstitial cell growth around vessels and between myocardial fasciculi in a typical case of rheumatic fever that showed at autopsy verrucous endocarditis of the mitral valves and the aortic valves, and in all probability a fibrinous pericarditis. This paper will deal with the historical development of our knowledge of the myocardial Aschoff body and its pathology as related to rheumatic heart pathology in general.

Cadet de Gassicourt, (4), in his review in 1887 suggested that the inflammatory process in rheumatism starts in the depth of the muscular substance
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and is made evident by proliferation of interstitial tissue. In 1890 Krehl, (5), made the observation that in a case of acute verrucous endocarditis there were present in the heart perivascular infiltration, increase in connective tissue and changes in the coronary arterioles which are, in all probability, the lesions at present receiving considerable recognition; this process occurring more frequently in the left ventricle, particularly under the auriculoventricular ring. Again Romberg, (2), noticed the preponderance of infiltration at the tendinous valvular insertion line and in the inner and posterior portions of the left ventricle. These observations of increased interstitial tissue and the presence of large cells are significant, as are also his descriptions of vascular involvement. According to Gross and Ehrlich, (6), Bret three months later published a more detailed description, referring to the cells as "embryonnaire", and observation which, in the light of modern conceptions on the origin of the Aschoff body, was quite remarkable. He observed enlarged pyknotic nuclei, a peculiarity in the staining properties of the cytoplasm, the occurrence of a caseous material surrounded by these large cells, all lying
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between the muscle fibers—in short, a picture that undoubtedly represents the type of Aschoff body of the coronal variety. The above mentioned men failed, however, to make what turned out to be the most critical and important contribution in the study of these lesions; namely, their recognition as a specific for rheumatic heart involvement. It remained for Aschoff to establish definitely the new era in the study of rheumatic fever when he announced that these lesions were specific for this disease.

As discussed by Gross and Ehrlich, (6), Aschoff in his 1904 report, based on a study of five cases of articular rheumatism from a collection of one hundred fifty hearts studied by Tawara, he observed the characteristic nodules in two. He described the simultaneous occurrence of blood vessel lesions simulating periarteritis nodosa, the submiliary size of these nodules, the tendency for the cells to assume fan and rosette arrangements around central necrotic areas, the large indented nuclei, the presence of giant cells and the peripheral zone of polymorphonuclear leucocytes and lymphocytes. He suggested the ultimate transformation of the nodules into connective tissue, thus predicting
future descriptions of the life cycle of the lesion, and believed the characteristic cells arose from leucocytoid elements derived from the adventitial cells of the blood vessels.

The following year Geipel, according to Gross and Ehrlich, (6), gave an excellent detailed description of his findings in the hearts from five cases of acute verrucous endocarditis of rheumatic origin. Believing the cells to arise from connective tissue this author was of the opinion that the "rheumatic poison" affects connective tissue with resulting cellular reaction and breaking down of collagen and cell cytoplasm. He observed that the nodules occurred in the fifth and sixth week after the onset of the disease, that they can reach a breadth of eighty microns and a length of eight hundred eighty microns, can occur in the interstitial as well as perivascular connective tissue, that the giant cells result from both multiplication of nuclei and confluence of individual cells, and that the ground substance evidently becomes fibrillar and transforms itself into connective tissue.

In 1907 Coombs, (7), described the Aschoff body, confirmed its specificity and added the observa-
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tion that the cytoplasm tended to be amphophilic. Again using Gross and Ehrlich, (6), Aschoff and Tawara in 1906 reported twenty-three cases and observed that the nodule did not bear as definite a relation to the blood vessels as had been stated before. They also added the description of the distinct nucleolus of the characteristic cell, mentioned the presence of mitotic figures and denied the origin of the giant cells from myocardium, mentioning the lymphocytoid cell as possibly giving rise to the characteristic cells. Gross and Ehrlich, (6), state that Bracht and Wachtler emphasized one of the most important histological properties of the cell cytoplasm; namely, its basophilia, and also laid stress on the subendocardial sites of these lesions. In his 1911 report Coombs, (8), stated that the ground work of the Aschoff body may contain fibrin, that the auricles are rarely the site of these lesions and that the papillary muscles and septum usually escape the rheumatic damage, whereas the central fibrous body and the tissue around it are especially susceptible to the inflammation. In 1914 Thalhimer and Rothschild, (9), again emphasized the specificity of the Aschoff body, mentioned the presence of several types of lesions in
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the myocardium, and described the "streamer like" processes of the cytoplasm.

In the same year Mallory, (10), described degenerated collagen fibers, which, being attacked slowly by endothelial leucocytes, may at times form giant cells.
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In considering diseases of the heart it is quite customary to take up the various anatomical elements of which the heart is composed; namely, the endocardium, pericardium and myocardium, and discuss the lesions occurring in each individually. I will follow this plan somewhat, but will discuss the pathology in a general way first.

Boyd, (11), states that the knowledge of the essential pathology in rheumatic fever has undergone a remarkable evolution in the past century and it is believed that the lesions produced are primary in the disease and not secondary as sequelae of the acute disease. Of late years the truth has begun to dawn that rheumatic fever is an inflammatory condition of fibrous tissues involving first and foremost the heart and, as a rule, the joints, the subcutaneous tissues, occasionally the brain and probably certain other organs.

In respect to the heart itself, interest was at first focused upon the characteristic vegetations along the line of contact of the valves and the accompanying pericarditis. The lesions in the myocardium were then discovered, and their effect upon the heart's action studied by means of the electrocardiogram.
Finally it was recognized that the essential valvular lesion was an inflammation of the entire valve, a valvulitis, and that the vegetations were to be regarded as merely incidental.

Boyd, (11), thinks the disease is gradually being considered as an indwelling infection, somewhat after the nature of syphilis and tuberculosis; the virus or offending organism sojourning for long periods within the body. The rheumatic nodule, the Aschoff body presently to be described, may be taken to indicate the continuance of the virus in the tissue in which the nodule is found. These nodules are encountered long after all acute manifestations of the disease have disappeared. Clawson, (12), for instance, records a case with old sclerosed valves in which active Aschoff bodies were found in the myocardium, yet five years had elapsed since an attack of rheumatic fever. The sclerosis of the valves was doubtless due to the original inflammation, but the potential agent capable of exciting that inflammation was still residing in the body.

In considering the pathology of rheumatic heart disease one is apt to consider only the particular lesions in the pericardium, the myocardium and valves.
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To really consider it thoroughly one should include all the tissues involved, but since this paper deals with the heart pathology primarily, that is all which will be considered. The principal lesion is the submiliary nodule, so called because it is smaller than the miliary nodule of tuberculosis; it being rarely visible to the naked eye.

The submiliary nodule is studied to best advantage in the myocardium. Swift, (13), has pointed out that there are two main types of lesions in rheumatism; the one proliferative and the other exudative, the former being the essential lesion. It is because the myocardial lesions are singularly free from the complicating exudative factor that they are so suitable for study.

The typical pathological unit is a submiliary nodule; variation in location, size and stage of development of these nodules account for most of the pathological pictures. The earliest evidence of injury is a fibrinoid swelling of the ground substance of the connective tissue. This substance stains like fibrin, and these fibers usually remain intact, but not infrequently small areas of fragmented fibrils are seen. In this
early stage wandering granulocytes are encountered. In from ten to fourteen days these areas are surrounded by the characteristic cells of the rheumatic nodule. McEwen, Bunin and Alexander, (14), have shown that these cells, obtained at biopsy from subcutaneous nodules, are not phagocytes, hence are neither monocytes, clasmaticocytes nor epithelioid. They possibly arise from undifferentiated mesenchymal elements of connective tissue, but they may originate from other cells as yet not highly differentiated. The granulocytes may persist and a few lymphocytes and plasma cells appear; usually the nodular cells gradually elongate and assume the appearance of fibroblasts, until a scar is formed.

Cecil, (1), states the myocardial Aschoff body is the most typical rheumatic granuloma; comparable lesions elsewhere are modified by the structure of the tissue involved. Therefore, subcutaneous nodules probably are conglomerations of submiliary granulomata occurring in structures capable of responding more vigorously to local tissue injury than is the myocardium. Similar submiliary foci are seen in the periarticular tissues and synovial membranes, but there is, in
addition, a marked increase in viscid synovial fluid containing fibrin, clasmatocytes and wandering cells, and the periarticular tissues are diffusely edematous.

In rheumatic pericarditis and pleurisy the exudate is serofibrinous. In the former the fibrinous characteristics may be very marked, and the normal endothelial covering may be entirely destroyed and eventually replaced by organization of the exudate into fibrous tissue with partial or complete obliteration of the pericardial cavity. Pericarditis in rheumatic fever is practically always accompanied by myocarditis, hence the importance of its detection.

Rheumatic valvulitis, ordinarily called endocarditis, is more clearly understood if considered from the viewpoint already advanced. In the gross there is a deposit of small grayish-pink verrucae along the surfaces of the valves at the lines of contact of opposing cusps, together with thickening of the valves. Microscopically, the vegetations consist of fibrin enmeshing various cellular blood elements deposited on a portion of the valve from which the endothelium has been denuded. In the substance of recently involved valves, as yet practically free from verrucae, there are at times areas closely
resembling Aschoff bodies. Small foci of proliferative inflammation with rapid vascularization are usually seen. It is, therefore, probable that the interstitial inflammation of the valve is the primary process and that the thrombotic verrucae are secondary in nature. The location of these verrucae is probably due to the mechanical trauma which causes the valvular endothelium, already swollen and proliferated because of the underlying inflammation, to be destroyed at the points of most violent impacts of the opposing cusps.

Cecil, (1), has shown that interstitial valvulitis is present in the majority of valves of the left side of the heart of patients dying from rheumatic carditis, and in about one-half of the valves of the right side of the heart. The healing process is effected by the vascularization of the verrucae and by scar formation in both the valve and vegetation; the endothelium at the bases of the verrucae grows over the surface and a thickened, scarred, less flexible valve is the usual result. The valves of a patient who has suffered from two or more attacks of rheumatic fever show evidence of the previous attacks in scar formation and increased vascularity, and of the last attack in new
focal proliferative lesions and recent vegetations.

Rheumatic granulomata not infrequently occur under and in the mural endocardium, especially in the left auricle of the heart. They have also been described to occur in the aortic adventitia, with small focal scars in the media and collections of granuloma cells about the vasa vasorum. In many visceral blood vessels inflammatory lesions have been seen.

Karsner and Bayless, (15), have shown that rheumatic fever frequently produces inflammatory and fibrotic lesions of the coronary arteries, although these lesions are not specific. The adventitia is often infiltrated with large mononuclear cells. The most important lesion is an intimal fibrosis of early life, thus producing precocious coronary sclerosis and narrowing of the lumen which may cause severe myocardial damage. This abundant myocardial scarring and progressive myocardial disability is better explained by coronary narrowing than in any other way.

Swift, (13), states that changes in the blood vessels are common. One often encounters partial or complete closing of the lumen with thrombi that have probably been formed as a result of injury to the vessel
wall. There are other ways in which the blood vessel may be constricted. Swift, (13), has seen Aschoff bodies in the perivascular space compress one segment of the wall against another. When two or more submiliary nodules are close together but on different sides of the blood vessel the edema, often present in the region of such foci, probably forms a constricting ring. Endarteritis, with swelling and proliferation of the endothelium as well as of the other intimal cells, is not infrequently seen in the smaller branches of the coronary arteries. This interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of the impulse-conducting fibers supplied by the involved blood vessels. Swift, (13), in a series of bedside studies and electrocardiographic studies of patients, discovered that myocardial or conduction system disturbances were encountered in ninety-five percent of the cases. He concluded that it is conceivable that these functional disturbances may have been merely toxic in origin. It seems more rational, however, to conclude that there is a direct relationship between the histopathological lesions demonstrable at post mortem, and the disturbed myocardial function found
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during life.
THE TYPICAL LESION — THE ASCHOFF BODY

Gross and Ehrlich, (6), have described what they term the life cycle of the Aschoff body in the myocardium. Depending on the shape and character of the lesion, they recognized coronal, reticular and polarized forms. There appear to be three stages in the development of the Aschoff body: (1). An initial phase up to the fourth week of the illness in which the lesions are of the small cell coronal and reticular types. (2). A middle phase from the fourth to the thirteenth week with large cell coronal, syncytial coronal, mosaic and polarized forms. (3). A final stage from the ninth to the sixteenth week with polarized and fibrillar forms. As the life cycle proceeds, the lesion tends to become elongated and finally fibrosed.

Gross and Ehrlich, (6), suggest the following classification:

1. Small cell coronal type,
2. Large cell coronal type,
3. Syncytial coronal type,
4. Reticular type,
5. Mosaic type,
6. Polarized type,
7. Fibrillar type.
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In the description of these types of Aschoff bodies mention will be made of their form. Some doubt may naturally arise as to whether this may not be influenced by the plane through which the sections are taken, or if it is actually so differentiated. Gross and Ehrlich, (6), have based their conclusions on a reconstruction of the shape of the Aschoff body gathered from observations of the lesions, as observed in a great many sections and, in some cases, on the study of serial sections. From their studies they conclude that the nodules, while at times spherical, are generally oval, disk-like or spindle in shape.

1. Small cell coronal type: This type of Aschoff body is generally somewhat oval in shape. Early in its development one may note in many examples of this type of Aschoff body a considerable accumulation of rather small cells—slightly larger than a lymphocyte—which form a generally compact mantle of varying thickness around a central mass of swollen eosinophilic collagen. Because of this peripheral situation of the cells with respect to the central collagen mass, this type of Aschoff body is referred to as the coronal type.

The nuclei may occur in three forms commonly
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found in all varieties of Aschoff bodies. The type of nucleus found most frequently, however, in the small cell coronal Aschoff body is round or oval with a delicate, sometimes folded nuclear membrane and a fine dust-like chromatin structure, which may at times show irregular concentrations or bar-like arrangements with fine projections radiating from the bar. The next most frequently occurring variety is the owl-eyed nucleus. Whitman and Eastlake, (16), refer to this as the "target nucleus". It is generally somewhat irregularly circular, possesses a heavy nuclear membrane with a distinctly dark and, at times, somewhat stellate nucleolus. In a much smaller percentage of the cells the nucleus is somewhat polymorphous in shape and generally quite large.

The cells in this type of Aschoff body may be so numerous, and the collagen at times so scanty, that the impression given is that of a rather compact cellular subvariety. This type of Aschoff body not infrequently shows a fairly conspicuous mantle of leucocytes among the other layers of the small cells, spreading diffusely into the adjacent myocardium.

2. Large cell coronal type: This type of
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Aschoff body is quite similar to the small coronal type in its morphological makeup. In this type the incidence of giant cells is larger than in the small cell coronal variety. This cell is characterized, as are the cells in most types of Aschoff bodies, by a central position of the nuclei. In this type of Aschoff body the giant cells are larger and many possess seven or more nuclei; the latter are round or oval and are irregularly arranged at the center of the cell.

3. Syncytial coronal type: This type of Aschoff body occurs relatively infrequently and has been found thus far generally in acute cases. The conspicuous feature of this lesion is the development of an enormous syncytial mass or masses, which apparently overshadow the scant central collagen material. The cytoplasm is extraordinarily abundant, basophilic, with indistinct ragged edges. The nuclei are predominantly of the owl-eyed variety and appear to take a peripheral position within the cytoplasmic masses.

4. Reticular type: This type of Aschoff body arises in loose connective tissue. It is found in its more characteristic form as a meshwork which shows an orientation directed more or less along the planes of
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the adjoining myocardial bundles.

5. Mosaic type: This type of Aschoff body is the kind most frequently encountered in the myocardium of the rheumatic heart. In contrast to the coronal types it consists of a more or less uniform distribution of collagen fibers and cells forming a mosaic pattern of the two components. In one form the cells seem to be squeezed into the spaces between the collagen masses with the cytoplasm extending as streamers, which are very delicate, between the more dense and somewhat solid appearing swollen eosinophilic collagen ground substance. In another variety of the mosaic Aschoff body the cells do not show the tendency to be compressed by swollen collagen masses. Both the cytoplasm of the cells and the collagen show considerable fragmentation, and they may become fused as in the reticular type. A prominent silver staining lattice is invariably present. It is this variant of the mosaic Aschoff body that is loosely designated by some as the "typical" Aschoff body. Giant cells are infrequently found.

6. Polarized type: This type of Aschoff body seems to represent a further stage in the metamorphosis of the Aschoff cells into fibroblasts. The general
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appearance of the lesion as a whole is that of a spindle shaped, tapering, disc-like mass representing many cells compressed between the myocardial bundles. The cells themselves vary from somewhat irregular elongated forms to spindle shapes, the variance probably being connected with the maturity of the lesion.

The collagen framework is generally delicate. While eosinophilic swollen fragments may be found, the fibers show, as a rule, less swelling than in the other types. The swelling and fragmentation may, however, at times be very noticeable and conspicuous.

7. Fibrillar type: This last stage in the evolution of the Aschoff body before it becomes transferred into an interfascicular scar may be properly referred to as the fibrillar type. The cells have definitely elongated themselves and approached the characteristic of fibroblasts. The nuclei are now predominantly of the fibrocytoid variety, although other types may still exist. The incidence of giant cells has become very small, whereas pyknotic nuclei are seen as often as in the mosaic types. The collagen has almost lost its eosinophilic swollen appearance and is represented by varying amounts of parallel, more or less isolated
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delicate fibrils with a rare swollen fragment. In the further evolution of the fibrillar Aschoff body, difficulties may be encountered in differentiating it from a somewhat cellular scar. The presence, however, of a giant cell and, here and there, of a ragged edge to the cytoplasm or blunt tip to the cell, and the presence of fibrocytoid or other characteristic nuclei are sufficiently characteristic to identify it as an Aschoff body.

This entity of proliferated cells is known as the Aschoff body. Boyd, (11): The bodies vary greatly in size; there may be only a few cells within the body, or it may be visible to the naked eye. The body may be round or it may be, as it frequently is in the myocardium, elongated or lemon shaped. The body bears a definite relationship to the adventitia of the small branches of the coronary arteries, lying alongside the wall of a vessel as it runs in the interstitial tissue between the bundles of muscle fibers. The cells of the Aschoff body are mainly the result of local proliferation, but some of them may also be regarded as arising from the exudative type of reaction. This is particularly true of some of the small round cells and certainly the polymorphonuclear leucocytes.
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Such are the essential features of the Aschoff body, the submiliary nodule as it occurs in its purest form in the myocardium.
SPECIFIC LESIONS

In 1926 Sacks, (17), published his excellent review on the pathology of rheumatic fever in which he suggested the subcutaneous nodule as a fruitful source for studying the origin of these cells by means of supravital staining technique. He considered these cells as possibly arising from histiocytes.

THE MYOCARDIAL LESION

In fatal cases of rheumatic carditis, the ventricular chambers are generally found dilated, even if death occurs after the first attack and the accompanying endocardial or pericardial inflammation be slight in degree. The dilatation is more pronounced on the left side than on the right and includes the auriculoventricular rings, especially the mitral. Whitman and Eastlake, (16), in 1896 were the first to recognize that mitral insufficiency in early rheumatic carditis is more often myocardial than valvular. It is quite a difficult task to prove that stretching of the aortic ring really occurs, but there are a few clinical observations that suggest such a possibility. Coombs, (7), believes that hypertrophy sets in while the signs of the acute invasion
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are subsiding. Dilatation and hypertrophy are the result of invasion of the myocardium itself, since they develop even if the heart is not embarrassed by valvular disease or pericardial adhesions. Sacks, (17), states that when mechanical factors are superadded, the heart, as might be expected, undergoes further stretching and increase in weight. In a large number of cases, Sacks, (17), found that the myocardium did not show very marked deviation from the normal when merely observed with the naked eye.

Sacks, (17), finds that the essential lesions are those in the interstitial tissue—the Aschoff bodies. These structures are rounded, globular, fusiform or spindle-shaped inflammatory nodules located in the interstitial tissue in close relation as a rule to the coronary arterioles. Most of these lesions are microscopic in size, but occasionally they may be seen with the naked eye. It has been reported that in one case there were numerous small pearly-white foci scattered especially in the muscle near the auriculoventricular ring which, on microscopic examination proved to be the typical Aschoff body. These nodules are situated mainly in the subendocardial tissues, but they are also present in
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the subpericardial layer of the myocardium as well as in its more central portion. As stated before they are more abundant in the left ventricle than in the right and occur especially in the basal portions; sites of predilection being the insertion of the ventricular wall into the fibrous ring of the mitral valve, the myocardium near the origin of the aorta, the apex close to the septum, and the interventricular septum near the base. In the right ventricle they are most likely to be found in the muscle bordering on the fibrous ring giving origin to the tricuspid flaps.

In cases of long standing rheumatic fever, which are principally valvular, and in which the presence of fresh vegetation reveals the existence of active infections, the nodules are less likely to be found than in cases which have proved fatal after the initial attack or before the disease has lasted many years. The number of nodules in a given case varies within wide limits. In endeavoring to find them, it may be necessary to examine considerable tissue before any are discovered, whereas in other cases nodules are found in abundance in almost every section, and between these extremes there is every degree of variation possible.
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Sacks, (17), states and describes the nodules much as does Boyd, (11). Sacks, (17), states the nodules consist essentially of the characteristic large cells which are arranged around a central necrotic zone in which there may be a little fibrin. The typical cell is a large polygonal element, containing one or more nuclei. The cytoplasm in hematoxylin-eosin sections is deeply dyed, finely granular and basophilic, and when stained by the Anna-Poppenheim method with methyl-green-pyranin, assumes a distinctive brilliant red color. The nucleus is polymorphous and vesicular and exhibits a finely defined nuclear membrane with one or more nucleoli, the greater part of the nucleus being clear and at times presenting a vacuolated appearance. These large multinucleated cells differ from the Langhans cells of tuberculosis in the central arrangement of their nuclei and resemble the Dorothy Reed cells of Hodgkin's disease. The number of these large cells in the Aschoff body is very variable; at times there are only a few and then at other times they may comprise as many as half. Mitoses in these bodies have not been encountered according to Sacks, (17).

These nodules may also and do develop in the
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adventitia of the coronary arterioles, in the periadventitial tissue, or at some distance away from the vessel wall. The nodule may approach the vessel at only one point in its circumference or may spread out in both directions until it surrounds half or even the whole of the circumference. The close proximity of the nodule to the vessel may lead to the compression of the lumen, especially when there are two nodules at opposite poles of the circumference. The interstitial tissue about the nodules is often edematous, and some of the surrounding muscle fibers may undergo degeneration.

The exact length of time required for the development or the disappearance of these nodules has not been determined. However, judging from the life cycle of the subcutaneous nodules, which are the homologues of the Aschoff bodies, one may be led to conclude that many may last for months or even years. It is also possible, as stated elsewhere, that the virus or infecting agent of rheumatic fever may be present in the nodules, producing fresh lesions from time to time and helping to perpetuate the infection in the body. As the Aschoff bodies grow older, the cells become elongated, their nuclei stain less sharply, the cytoplasm becomes acidophilic
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and the cells are finally converted into a homogeneous necrotic mass. As the large cells disappear one finds that fibroblasts are making their appearance. These nodules are finally replaced by scar tissue, in which a few lymphocytes may persist for a long time. Broad parietal scars are very characteristic of the healed stage.

The origin of the large cells of the Aschoff body has often been discussed. Some authors state they are derived from the myocardium, Whitman and Eastlake, (16). But the presence of identical cells in regions where muscle is absent; e.g., the valvular or auricular endocardium makes it difficult to accept this origin fully and completely. It is the opinion of most observers that these Aschoff cells are derived from adventitial or connective tissue cells, Aschoff, (18), or from endothelium, Coombs, (7). The problem of the exact origin of the cells which make up the nodules is still controversial and seems at the present time to be centered about the source of the histiocytes.

Sacks, (17), states that it is important to note the rheumatic virus, if the infecting agent be a virus, may invade the myocardium without injuring the
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valves, and clinically this fact is of great importance. In other cases the endocardial or pericardial involvement may be negligible, but the degree of ventricular dilatation and the severity of the cardiac symptoms in general testify to the profound disturbance which may result from the localization of the rheumatic virus in the myocardium itself. Such have been the findings in a few cases, but there have been but few reports of cases of proved rheumatic myocarditis in which the valves were entirely free of either recent or old disease.

The conspicuous alterations, so frequently found in the rhythm of the heart during the course of rheumatic fever, must be based on heart-block. Heart-block in its various stages, from slight prolongation of auriculoventricular conduction time to partial or even complete disassociation, is the most frequent alteration noted. There have been other alterations or abnormal rhythms reported; e.g., premature contractions, nodal rhythm, auricular flutter and fibrillation, paroxysmal tachycardia, and sinoauricular block. If the electrocardiograms of the patients suffering with rheumatic heart disease be observed, there is evidence that the heart is affected in about ninety-five per cent of
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the cases, Sacks, (17). These changes are frequently slight and usually transient, even if they be severe. Cohn and Swift, (19), believe that they may be explained by the presence of the Aschoff nodules, circumnodular edema, and perhaps of the ischemic areas consequent upon blood vessel involvement.

ENDOCARDIAL and VALVULAR LESIONS

Sacks, (17), states that rheumatic endocarditis is more frequent in the valves of the left side of the heart than in the right side, but the incidence of tricuspid involvement is higher than usually considered. In a series of eighteen cases of endocarditis with Aschoff bodies in the myocardium, he also discovered fresh vegetations on the tricusps in twelve cases—or sixty-six and six-tenths per cent. Coombs, (7), noted tricuspid disease in thirty-six per cent of cases with rheumatic carditis. It is probable that organic insufficiencies and stenoses of the tricuspid would occur more commonly than they do, were it not for the fact that the rheumatic vegetations are frequently implanted upon a limited segment only of the circumference of the
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Sacks, (17), states that the appearance of the vegetations in rheumatic carditis is typical. They take the form of minute cauliflower or wort-like forms, one to two mms. in diameter, and are generally of uniform size, pinkish-gray, grayish or grayish-white in color and are situated along the line of closure of the valves. At times these vegetations may be polypoid and larger. It has been reported that in rare instances these verrucae extend for short distances along the chordae tendineae, Coombs, (7). Sacks, (17), further states that the surface of the vegetations in the early stage of their development is dull and opaque, and somewhat later they may present a glistening appearance. The valve leaflets themselves may appear slightly pink and swollen. The entire line of closure of the given valve may be covered with vegetations and this is the rule in the mitral valve, but in the aortic valve and especially in the tricuspid valve only a part of the valves may be affected, Libman, (20). The above fact may be the explanation for the greater frequency of mitral valve stenosis and regurgitation than similar involvement in the aortic and tricuspid valves. The vegetations have
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a rather tough consistency, being relatively difficult to crush, and they adhere very tenaciously to their point of attachment to the valves.

Swift, (21), in his study of four cases of rheumatic fever, dying within two or two and one-half weeks of the onset of the arthritis, discovered the following: In three the attack was the first, and in the fourth death occurred during the second attack. Aschoff bodies were found in the substance of the valve, and there were in addition interstitial edema and a diffuse proliferative valvulitis reaction. These changes occurred in valves or portions of valves which were free of verrucous deposits, suggesting that endothelial injury is not primary but secondary to the interstitial valvulitis. Swift, (21), also contends that the rheumatic verrucae are due to the deposition of thrombi on portions of inflamed valves where the vitality of the endothelium has been impaired by repeated impacts with the contiguous valve, but he also thinks it possible for the verrucae to form at a point where the submiliary nodule breaks through the surface of the endocardium. If these findings be correct, and they apparently are, Sacks, (17), would suggest that the virus of rheumatic fever is
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brought to the valve by way of the intrinsic vessels, and the demonstration of blood vessels of non-inflammatory origin in a certain percentage of hearts other than those of the fetus, Kugel and Gross, (22), shows that this method of infection is anatomically possible.

Libman, (20), states that these vegetations show healing at an early stage. Blood vessels and fibroblasts invade the verrucae, and these finally become cicatrized. Von Clahn and Poppenheimer, (23), have demonstrated that hyaline material may be found on the surface or within the substance of the valve for a long time after healing has taken place. Sacks, (17), states that the final development of mitral stenosis from a row of vegetations on the line of closure is quite remarkable, and he had no good way of explaining the same. He does state, however, the fact that inflammation of the valves is not only an endocarditis but also a valvulitis, with extension of the inflammation far beyond the region of the attachment of the vegetations. This will to some extent explain considerable which otherwise would go unexplained.

Sacks, (17), further states that the rheumatic infection tends to recur, but the manifestations of re-
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currence need not be present each time in a clinical manner. He states that it has been proved that mitral stenosis of the typical rheumatic type may reach its full development without satisfactory history of rheumatism. He has found that it is not at all unusual to discover active infection at postmortem examination when none at all was expected during life. It is, therefore, possible to find fresh verrucae on chronically diseased valves, when clinically the infection was considered obsolete, and the examination of the most thickened and deformed valves frequently reveals deep cellular infiltrations of wide extent of Aschoff bodies.

MacCallum, (24), was the first to describe the Aschoff body in the left auricle. He described the lesion as follows: "The lesion is located on the wall of the left auricle, extending upward from the root of the posterior leaflet of the mitral valve in the form of a corrugated or puckered patch of endocardial thickening, sometimes being covered with a thin fibrous layer".

Mac Callum, (25), also noted that at times there were distinct projections on the auricular surface resembling very much the vegetations on the mitral valve itself.

Sacks, (17), states that on microscopic exam-
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Ination of the more acute lesions, the lining layer of the auricle is spread apart by edema and an extensive accumulation of exudate cells of all sorts may occur, including mononuclear cells, polymorphonuclear leukocytes, and occasionally a few eosinophiles. The most striking feature, however, is the presence of numerous large Aschoff bodies which are forced into rows by the arrangement of the elastic tissue lamellae, so that the Aschoff bodies have a banded appearance, MacCallum, (24). According to Von Clahn's, (23), description, the greater number of the Aschoff cells form a palisade along a band of hyaline material, their nuclei being perpendicular to the band. As the healing process progresses the endocardium is invaded by capillaries and fibroblasts, the characteristic cells disappear, and finally a dense avascular scar develops which may at times be infiltrated with calcium salts.

PERICARDIAL LESIONS

According to Boyd, (11), rheumatism is the commonest cause of acute pericarditis. There is very little that is characteristic of pericarditis in the
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acute stage of rheumatism. The fluid is serous—an exudate from the serous membrane—and is never purulent.

The chief element is the fibrin, which is deposited on both surfaces of the pericardium, giving it a very shaggy appearance. Even if no fibrin is seen, the natural gloss of the membrane is lost.

In the microscopic picture one finds that the endothelium has been cast off, successive layers of fibrin have been laid down, and organization by invasion of new blood vessels and fibroblasts has taken place. One will find that the inflammatory cells are mostly lymphocytes and plasma cells with very few polymorphonuclear leucocytes. This inflammation usually extends through the subpericardial fat down to the heart muscle itself.

The after-effects, according to Boyd, (11), may vary considerably. There may be merely one or two opaque white patches of thickened epicardium known as "white spots", or if the absorption of the exudate is less complete there may be numerous adhesions. And lastly there may be a completely adherent pericardium. There is also a possibility of the parietal pericardium becoming fixed to the mediastinum and chest wall, so that the
heart may become pinned down and as a result render contraction impossible, and the result would be chronic invalidism and death. These areas may also become calcified and form stony plates on the surface of the heart.

Sacks, (17), states that fibrinous pericarditis, as found in rheumatic fever, is generally accompanied by myocarditis and endocarditis, but in a few cases endocarditis has been absent. If one scrapes the fibrin off the above described lesion, the serous membranes are seen to be hyperaemic and often ecchymotic.

On further examination the edematous subpericardial tissues are seen to be invaded by numerous capillaries and fibroblasts and exhibit a diffuse cellular reaction, with concentration of the cells about the blood vessels. These vessels according to Sacks, (17), frequently show endothelial swelling and proliferation, with or without thrombosis, and are often thickened as a result of the deposition of hyaline-like material.

The pericardial Aschoff bodies are often quite large and are most frequently found in characteristic form during the period of organization of the pericarditis. Swift, (13), states that the essential or primary pathological process is similar to that found elsewhere but that the
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gross appearance is altered by the peculiar anatomical structure of the pericardial sac, and the manner in which such large endothelial membranes respond to injury.

Poynton, (26), in 1899 discovered the following very interesting things in a case of rheumatic pericarditis and extreme dilatation of the heart. During the acute stage of the disease there was a general continuous pericardial friction rub and this was a strong indication against a large effusion, but he, nevertheless, expected an effusion and took especial care in opening the chest in order to save the fluid. He was disappointed, however, because the pericardium was generally adherent, and the enlargement almost entirely due to the dilated heart, and slightly to the thickening of the pericardium. The pericardial adhesions were firm at the sides, behind the adhesions were quite recent, and the pericardium at places swollen to the thickness of half an inch. The new or recent adhesions were in the form of flakes of lymph, in the interstices of which was a little fluid. The lungs were adherent to the pericardium as well.

Poynton, (26), also made microscopic studies
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of the pericardium and the nodules in the above case. In the section through the pericardium extreme vascular dilatation and plastic inflammatory exudation into the pericardial cavity was shown. In the wall of the ventricle there was a similar but slightly less marked capillary distention, and both under the pericardium and far away from it there was a free exudation of small cells between the muscle fibers. The above findings were in an acute case which terminated fatally in a month. In cases of longer standing one finds an adherent pericardium and often fixation as previously described.

There has been some disagreement about the possibility of a pericarditis without a myocarditis and visa versa. Poynton, (26), arrived at the conclusion, from microscopic studies, that when pericarditis is present the myocardium is also affected concurrently, for the changes in the heart walls commence by numerous scattered foci, some of them far from the pericardium, and the changes in the muscles are general.

Sequeira, (27), in discussing pericardial adhesions, stresses the possibility that the contracting bands, (bands of adhesions), may compress the great
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vessels, and especially the veins. In one case he saw the left auricular appendix so bound down that its cavity was almost obliterated. In cases of adherent pericarditis he noticed tags attached to both layers of the serous pericardium, and these tags were evidently fragments of adhesions broken off by the constant movement of the heart, and at the apex, due to its greater amplitude of movement, the adhesions were pulled out to an inch or two in length.

On more thing must be considered and that is pericardial dilatation; a direct result of rheumatic fever. In normal health the pericardium tends to be a restraining covering for the heart. When the pericardium, therefore, becomes diseased and dilated this feature is lost, and as a result the heart will gradually become dilated and tend to fill the lately developed enlarged envelope or pericardial sac. The now dilated heart is weakened and is more subject to future intoxication and disease.

CONDUCTION MECHANISM LESIONS

Aschoff, (16), in 1906 delivered a paper at
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the University of Freiburg in which he discussed heart-block to some extent. He first gave credit to the Leipzig school for having drawn attention to the frequency with which alterations in the myocardium occur when there is hypertrophy, especially in cases of valvular disease, and also in acute infectious diseases. Dr. Tawara was Aschoff's assistant in the experimental work. They examined one hundred twelve hearts, among which were twenty-four cases of valvular disease of rheumatic origin. To their surprise the inflammatory changes were quite insignificant. There were, however, in a percentage of the valvular diseased cases, recently acquired interstitial alterations to be found. These were, for the most part, quite specific in rheumatic affections in that the peculiar submiliary nodules were seen to have developed both in the interstitial connective tissue, especially in that surrounding the arteries, and in the subendothelial connective tissue layers.

Aschoff, (18), does, however, doubt that these small nodules fully account or are responsible for the marked cardiac weakness in these patients. In the great majority of cases of valvular disease, they found no fresh inflammation at all, but only more or less numer-
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ous, very small, perivascular, fibrous nodules, which were the healed remnants of the original submiliary nodule. They found also that these intrude very little into the muscular substance proper, and, therefore, they concluded that likely they did not affect the cardiac muscle function to any great extent.

The impulse mechanism of the heart is considered to be as follows: The impulse begins in the sino-auricular node, which is situated in the right auricle, and this, also called pacemaker, sets up a generalized impulse over the auricles and conducts the impulse directly to the auriculo-ventricular node, and this in turn sends the impulse over the ventricles by left and right bundles. These bundles are a unit for a short distance distal to the auriculo-ventricular node before bifurcation takes place. Any lesion or obstruction along the pathway mentioned will cause a block, either partial or complete, depending on the lesion or causative factor producing the same.

Aschoff, (16), and his associate made a microscopic study of these pathways. They found these fibers sharply distinguished histologically from all the other muscle fibers, not only by a difference in size, but
more especially by their pale color in stained preparations due to decreased amount of fibrillar substance, and by their well marked connective tissue sheath. These they followed to their terminations into the ventricular muscle. Another important finding was the fact that these were found in the ventricles only.

Now, it is quite certain that by disturbances in the main trunk irregularities in the heart may be brought about, but can inflammatory lesions in the smaller branches account for any irregularities? Aschoff, (16), believes that they may if extensive enough. He goes on to state that the fibers of the conducting system do not show hypertrophy like the other muscle fibers do in valvular disease, and as a consequence may be too small to carry the rhythmical action of the heart to the hypertrophied muscle.

They have found not infrequently, in cases of rheumatic myocarditis, actual destruction of the smaller and at times larger branches of the conducting system. The specific nodules, before described, have a special tendency to develop beneath the endocardium and at times directly in the connective tissue sheaths of the system. This multiplication of cells finally destroys the con-
ducting mechanism and as a result we will have heart block because the continuity of impulse has been broken.

The fact that so often in rheumatic affections the inflammatory changes run their course less in the cardiac muscle than in the subendocardial layers, makes it perhaps possible and understandable, that, in spite of no specific ventricular muscle alterations, inflammatory destruction of the subendocardial conducting system over an area may cause irregularities and heart block.

Aschoff, (18), comes to the conclusion that it is only when a wide area of the conducting system is destroyed or when the ventricular portion is permanently destroyed or separated from the auricular portion by destruction of the main trunk or a specific lesion in the auriculo-ventricular node, there is danger of sudden or gradual heart-block with heart failure. This is the only reference I was able to find which gave in any way a descriptive pathology of what was and is responsible for heart-block in rheumatic fever. I shall discuss a few other views and experimental work, but they do not give a definite pathological picture. They merely state a fact and a condition without giving any clear cut
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pathology for the same.

White, (28), in 1916 discusses a case of rheumatic fever in which heart-block was the first sign. The case was a boy of eighteen years who complained of palpitation without any specific complaint of joint pain. There were many dropped beats. The patient was put on salicylates and in one month there were no more dropped beats, in six weeks there was a perfectly normal rhythm and a perfectly normal P-R. interval of 0.145 seconds. He came to the conclusion there was myocardial damage of an infectious nature and not organic.

Cohn and Swift, (19), after careful electrocardiographic study of patients, conclude that the nodule, as described by Aschoff, and perhaps the ischemic areas consequent upon blood vessel involvement underlie the disturbance in impulse conduction as recorded on the electrocardiograph. These men, however, have no explanation as to how extensive or how these nodules must be situated to produce the results.

Swartz and Weiss, (29), discussed a somewhat different phase when they studied auricular fibrillation in children. Between the fall of 1921 and spring of 1927 sixty children, ranging in age from five to fifteen,
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came under their observation and they all had chronic rheumatic cardiac valvular disease. All had definite histories of recurrences and exacerbations of the disease prior to admission, and in every instance there was advanced organic involvement of the heart. Ten of the sixty showed auricular fibrillation sometime during the period of observation. In six children the onset of the arrhythmia was noted during the acute phase of the rheumatic infection when the temperature was above the normal.

In discussing the possible cause or extrinsic factors which might be responsible for the auricular fibrillation, they dismissed them as insignificant in children. They did much the same with acute rheumatic carditis, but stressed the connection between mitral stenosis and the development of auricular fibrillation. There is a definite association between mitral stenosis and an arrhythmic pulse, and long before the mechanism of auricular fibrillation was expected the so-called "mitral" pulse had prognostic significance. They state that over thirty-five per cent of adults with mitral stenosis develop auricular fibrillation. All of their children in the above series had mitral stenosis. Now,
since we know that mitral stenosis is a direct result of rheumatic fever in a large per cent of cases, and since auricular fibrillation occurs in so many cases of mitral stenosis, may we not conclude that mitral stenosis is an important factor in the development of auricular fibrillation and, therefore, rheumatic fever is one of the underlying causes? Again these men give no real pathological picture, but I believe the above conclusion at which I have arrived is worthy of note.

Niehaus, (30), in 1937 discussed the occurrence of auricular fibrillation in rheumatic fever, but he, too, did not give a very satisfactory discussion of the pathology involved. He does, however, give some interesting findings and I shall note a few of them. He accepts the circus movement of the auricles, as described by Lewis, as the plausible basis for the mechanism of auricular fibrillation. He further states that the chief types of heart disease associated with fibrillation are (1) rheumatic fever or rheumatic heart disease, (2) myocardial and hypertensive disease, and (3) goitre. The first two are quite closely united at times, so we see that fibrillation is closely tied up with rheumatic heart disease. In his experience in the rheumatic group,
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fibrillation occurs between the ages of thirty to forty. Parkinson and Campbell, (31), in 1930 stated that fifty-six and eight tenths per cent of rheumatic hearts fibrillated between thirty and forty-four years of age and seventy-five per cent between twenty and forty years. They did not give a very satisfactory pathological explanation, however, of what causes these hearts to fibrillate.

Niehaus, (30), confirms the report of Swartz and Weiss, (29), in stating that mitral stenosis, of all valvular lesions, is most frequently complicated by fibrillation. He is of the opinion that the auricle becomes distended because of the mitral stenosis and this may interrupt or disturb the mechanism sufficiently to cause fibrillation. At any rate, he considers auricular fibrillation as indicative of quite advanced heart disease.

Bruenn, (32), has another rather interesting explanation for the occurrence of auricular block. He made a study of twenty-two cases of acute rheumatic fever with marked evidence of impairment of auriculoventricular conduction in the electrocardiogram. The degree of the block varied from a prolongation of the
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P-R. interval above 0.2 seconds to incomplete block. To all of these he gave atropine to the safe limit and found a marked decrease in the conduction time with an increase of twenty-six and four tenths beats per minute on the average. He also noted that in general the greater the degree of block before giving atropine, the greater the decrease of the P-R. interval following injection of the drug.

Atropine counteracts the effect of vagal stimulation and therefore he concluded that the vagal tone plays a very important part in the production of impairment of auriculoventricular conduction time in cases of acute rheumatic fever. This has been substantiated by other workers.

I have now put forth two quite different schools of thought on the subject, and neither one answers the question completely because they have not produced specific pathology to substantiate their views. There is still much to be done in a pathological way in this field of auriculoventricular conduction impairment.
SUMMARY and CONCLUSIONS

(1). We know the incidence of rheumatic heart disease is still very high in spite of a fall in the incidence of rheumatic polyarthritis.

(2). Romberg, in 1894, was the first to describe the inflammatory lesions found in the myocardium of patients suffering from rheumatic heart disease. But it remained for Aschoff to establish the fact that these lesions were specific for this disease; following which these lesions have been known as Aschoff bodies.

(3). These lesions are believed to be primary in the disease and not secondary as sequela of the disease.

(4). The disease is gradually being considered as an indwelling infection somewhat similar to tuberculosis or syphilis; the offending organism sojourning within the body for long periods. This is borne out by Clawson, (12).

(5). Endarteritis, with swelling and proliferation of the endothelium is frequently seen in the smaller branches of the coronaries and this impairment of circulation leads to disturbed nutrition of the muscle tissue and of the impulse-conducting fibers which lead to heart weakness and conduction mechanism.
SUMMARY and CONCLUSIONS

disturbance.

(6). The lesions are most typical in the myocardium and it is these lesions which are best suited for pathological study.

(7). Dilatation and hypertrophy of the heart are the direct results of invasion of the myocardium itself. There is evidence of marked ischemia throughout the myocardium, probably due to the marked proliferation of the endothelium of the heart vessels.

(8). The valves of the left side of the heart are more often involved than are the valves of the right side. Therefore, we find mitral stenosis and regurgitation more often than tricuspid involvement of the same nature.

(9). The healing process is affected by the vascularization of the verrucae, which have formed on the valve, and by scar formation in both the valve and vegetation; the endothelium at the bases of the verrucae grows over the surface and a thickened, scarred, less flexible valve is the result. Yes, and further we find valvular stenosis and regurgitation a direct result.

(10). The fluid in rheumatic pericarditis is serous and is never purulent.
SUMMARY and CONCLUSIONS

(11). Pericarditis very often develops into an adherent pericarditis and often becomes fixed to the lungs, mediastinum or chest wall and so embarrasses the heart action. As the pericardium increases in size so does the heart, and as a result a weakened heart is produced which may lead to various types of faulty impulse-conduction time.

(12). There is a marked disturbance in the impulse-conduction mechanism in a large percentage of these hearts. The chief disturbances are heart block, either partial or complete, and auricular fibrillation.

(13). The exact cause and pathology involved in producing faulty impulse-conduction time in so many of these hearts is not known, but several ideas have been put forth with some proof for each. They are: (1) a definite organic lesion somewhere along the conduction pathway; (2) a toxic substance which acts directly on the impulse fibers and on the muscle fibers; and (3) increase in vagal tone.
BIBLIOGRAPHY


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